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Review

The role of obesity in the development of cardiovascular diseases: An overview of human and rodent studies

Obesity and cardiovascular diseases

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Abstract
Basically, obesity occurs when the amount of calories taken into the body is more than the amount spent in the long term. Treatments applied by reducing calorie intake and increasing movement do not always give positive results. This is because the etiological elements of obesity and the relationship between these elements have not been fully revealed. Factors that play a role in the emergence of obesity include limitation of movement, diet, genetic factors, smoking, psychosocial factors and insomnia. There are many common factors in the pathogenesis of obesity and CVD. In order to reduce the harmful effects of obesity, researchers are creating animal feeding protocols, especially rodents, and conducting studies that cannot be done on humans. The aim of this review is to briefly address two important interrelated issues that affect human health and life: the relationship between obesity and cardiovascular diseases. The review will also dicuss why rodent models are used.

Keywords
Obesity, Cardiovascular Diseases, Obesity And Rodent Models

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Introduction

In general, obesity is the occurrence of excessive fat as a result of the excess fat taken into the body, which creates health problems [1]. This disease is also the basis of cardiovascular diseases (CVD), type 2 diabetes (T2DM), hepatic steatosis, stroke, hypertension and some types of cancer [2].

Obesity was first seen and discussed towards the end of the 16th century [3]. Obesity levels initially appeared in countries with high economic levels. However, today it is a common health problem in countries at all levels of the economy [4]. In essence, obesity is a condition where the long-term calorie intake exceeds the amount of calories consumed by the body.[5]. Treatments applied by reducing the intake of these calories and creating behavioral differences (such as increasing movement) do not always give positive results. This is due to the fact that the etiological elements of obesity and the relationship between these elements have not been fully revealed [6]. Factors that play a role in the occurrence of obesity include limitation of movement, diet, genetic factors, smoking, psychosocial factors and insomnia [7].

Etiology

Obesity, which can start in any age group, occurs with insufficient movement in its etiology and an increase in the consumption of ready-to-eat food. It is due to its intake rather than energy expenditure. In other words, eating foods rich in carbohydrates and high in saturated fat causes obesity. In addition, endocrine disorders can occur due to weight gain triggered by some drugs used and hereditary reasons [8].

Adipose Tissue

In obesity, the stretching feature of adipose tissue is very high. It can even be called unlimited. They are expressed according to their composition, size, function and location. Mammals generally have two types of adipose tissue. White adipose tissue is the most abundant adipose tissue in the body. It can be found around organs and blood vessels in the abdominal cavity and under the skin. The excess energy is preserved in triglyceride structure because the main structure of triglycerides is predominantly composed of glucose. The rate of glucose uptake into adipose tissue is therefore critical in maintaining triglycerides. In addition, this condition plays a role in the likelihood of hypertension and cardiometabolic occurrence [9].

Brown adipose tissue makes up only 4.3% of adipose tissue in an adult human. Axillary, mediastinal, abdominal, paraspinal, cervical and supraclavicular are among the places where it can be found [10]. It has been determined that brown adipose tissue has both cardiometabolic and health-beneficial functions (anti-diabetes, anti-obesity and protection against hypothermia) [11]. In addition, there are interstellar brown fat cells found in newborns, which are deformed over time and are never seen again in adults [12]. A comparison of fat cells in humans and rodents is given in table 1 [13].

Body Mass Index

Body Mass Index (BMI) is a method used to find out if an individual is in a healthy weight range. Calculation of BMI; BMI = Weight (kg)/height^2 (m^2). Fat accumulation, especially in the middle/abdominal region, is an important health problem. Therefore, better results are obtained from waist circumference and waist-hip ratio calculations. Because waist circumference and waist-hip ratio are related to body fat distribution and central obesity. This relationship is also why it is associated with morbidity (14).

The Relationship Between Obesity and CVD

Obesity is linked to numerous cardiovascular system diseases, including pulmonary hypertension, stroke, and venous thromboembolic disease [16]. There are many common factors in the pathogenesis of obesity and CVD. In both cases, lipids, oxidized LDL particles and free fatty acids activate the inflammatory process, triggering the disease. Inflammation is

Table 2. Classification of Obesity in Adults According to BMI [15].

Classification of Obesity	Degree	BMI kg/m^2
Slim		<18.5
Normal		18.5-24.9
Overweight		25-29.9
Obese	1	30-34.9
Obese	2	35-39.9
Extremely obese	3	≥40

Table 3. High Risk Obesity, Cardiometabolic Risk Elements and Consequences [18].

OBESITY	
Cardiometabolic Risk Mediators	**Cardiovascular Outcomes**
Increase insulin resistance	Increase in cardiovascular events
Glukose intolerance	Increase in coronary artery disease
Type II diabetes	Increase in heart failure
Increase in blood pressure	Increase in arrhythmias
Increase in anormal lipid metabolism/dyslipidemia	Increase in arrhythmias sudden death
Increase in inflammation	
Endothelial dysfunction	

Table 1. Comparison of White, Brown and Beige Fat Cells in Humans and Mice [13]

Adipocyte Cell	Progenitor	Depots	Differentiation Obesity Stage	Function
White Adipocyte	CD24, CD34, PDGRFα	Subcutaneously, around majör organs and blood vessels in the abdominal cavity	Hypertrophy, secretion of vasoconstrictors, hyperplasia	Secretion of vasoactive factors and adipokines, stroge of trigliserit
Brown Adipocyte	Myogenic origin En-1, Pax7, Myf5	Thoracic PVAT, interscapular (only human babies)	Potentially resistant to inflammation caused by obesity	Thermogenesis, Cardioprotective, Anti-inflammatory properties
Beige Adipocyte	Vascular smoot muscle origin	Subcutaneous (only rodents), Thoracic PVAT, cervical, sublacilavicular paraspinal, axillary, renal	Loss of UCP1 expression, 'whitening'	Thermogenesis, Cardioprotective, Anti-inflammatory properties

CD, Cluster of differentiation; PDGFRα: Platelet-derived growth factor receptor alpha; Pax7, Paired box 7; En-1, Engrailed-1; Myf5, Myogenic factor 5; PVAT, Perivascular adipose tissue; Ucp-1, Uncoupling protein-1.

involved in many processes, from early endothelial dysfunction leading to atherosclerotic plaques and causing complications. Even, it plays a role in the entire process leading to CVD. Adipose tissue releases adipocytokines that induce insulin resistance, endothelial dysfunction, hypercoagulability and systemic inflammation, thereby triggering the atherosclerotic process and other CVDs [17], (Table 3) [18].

Sometimes, obese people may not have any other discomfort other than high BMI. This is called metabolically healthy obesity [19]. It has been proven that people who are metabolically healthy obese (MSO) may develop 'metabolically unhealthy obesity' in the future [20].

Discussion

Obesity plays an important role in the development of heart failure with preserved/decreased ejection fraction [21]. Studies have shown that overweight individuals are more likely to develop heart failure than thin patients; It has been proven that this probability is even higher in obese individuals [22]. Likewise, the relationship between the development of atrial fibrillation and obesity has been shown in many recent studies [23]. The tendency of people with MSO towards 'metabolically unhealthy obesity' within 4 years was found to be 43% in women and 46% in men. MSO people were also more likely to develop subclinical coronary artery calcifications. These people had a higher incidence of diabetes, CVD, and even death than people of normal body weight [19]. In a large, long-term study involving more than 6,000 individuals and lasting approximately 12.2 years, MSO was compared with metabolically healthy non-obese individuals. Metabolic syndrome was observed to develop in approximately half of MSO individuals [24]. In another study comparing metabolically healthy non-obese individuals with MSO individuals, it was revealed that the likelihood of heart failure, coronary artery disease and cerebrovascular diseases occurring in individuals with MSO was higher [25].

Positive results have been obtained in studies regarding waist/height ratio predicting other diseases, especially CVD [26]. By the European Society of Cardiology; It is recommended that waist circumference be <80 cm in women and <94 cm in men and BMI be between 20-25 kg/m2 [27]. According to another published data results, it has been suggested that waist circumference of 102 cm and above in men and 88 cm and above in women is related to central obesity and may also be linked to Type 2 DM and CVD [28]. In a study, it was suggested that BMI greater than 30 kg/m2, waist/hip ratio and waist circumference pose a CVD threat [29]. In the meta-analysis study conducted by Ashwell et al., it was proven that waist/height ratio is more effective in determining cardiometabolic risks than BMI and waist circumference in both men and women [30].

In short, studies continue to show that regardless of the level of obesity, it increases the likelihood of CVD [31].

Obesity treatment is carried out both in terms of diet, pharmacology and surgery. In terms of diet, weight loss is achieved with a high-fiber, low-fat, low-calorie diet [32]. The main purpose of nutrition is to ensure that the person reaches normal weight ranges. While doing this, CVD events should be eliminated by achieving the appropriate lipid level [33].

In order to reduce the harmful effects of obesity, researchers carry out studies that cannot be performed on humans by creating animal diet protocols, especially on rodents [34]. Because studies on obesity in humans are limited and clear results often cannot be obtained due to accompanying diseases such as hypertension and diabetes [35]. Efforts are being made to create obesity models on animals. However, there is no animal model equivalent to human metabolic syndrome [36].

If rodent models can be constructed in a way that is very similar to human obesity, it supports the view that more information can be obtained [34]. Since obesity plays a major role in the formation of many diseases, various studies have been carried out to reduce its negative effects. When these studies were examined, the protective effects of various chemical substances and extracts obtained from plants with antioxidant and lipid-lowering effects on obesity, especially their functions on heart health, were investigated. These studies include the research conducted on the Andrographolide component of Andrographis paniculata (King of Bitterness), which has been demonstrated to exert a strong anti-obesity effect on the expression of CCAAT/enhancer binding protein β, regulated by protein kinase A (PKA)-CREB (activation of cAMP response element binding protein) in adipogenesis of 3T3-L1 cells [37]. It has been suggested that administration of A. paniculata extracts may also prevent cardiovascular damage by inhibiting the expression of myocardial inflammation and apoptosis-related genes in obese mice fed a high-fat diet [38]. Vieira-Brock et al. fed the mice a high-fat diet (HFD). A mixture of thermogenic food ingredients, including dihydrocapsiate and paprika, alone and in combination with a whey protein supplement, was studied for its effects on body composition in mice. They showed that the mixture stimulated thermogenesis in mice and reduced body weight and fat gain in response to a high-fat diet. These effects have been shown to obtain the same result when applied in combination with whey protein supplementation [39]. In another study, neuroprotective effects were observed by providing green peanut supplementation to mice fed HFD [40]. It has also been proven to improve the lipid profile in obese patients [41].

Conclusion

Based on the information we present in our review, it appears that the likelihood of CVD occurrence increases with the formation and increase of obesity. In this case, threats that induce CVDs need to be either eliminated or reduced. Obesity is one of the main threats. New techniques and methods are needed to control obesity.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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